Remarks:

Claims

Claim Status, Support for Amendments

Reconsideration of the rejections is respectfully requested. By the present amendment, claims 38-42, 58 and 65 have been cancelled without prejudice to address 35 U.S.C. §112, second paragraph issues, and to more particularly define Applicant's invention. Applicant reserves the right to claim the subject matter of the cancelled claims in a continuing application.

Claims 57 and 61 have been amended. New claims 66-78 have been added. The number of total claims and of independent claims remains less than the amount for which fees were previously paid.

The claims have been amended to more clearly define the invention. Support for the new claims and amendments is either apparent, or is as described below. Support for the recitation of the phospholipids in claim 66 can be found, for example, at page 8, lines 16-26. Support for the recitation of second component in claim 66 can be found, for example, at page 13, line 29 through page 14, line 8; and at page 9, line 23 through page 10, line 3. Support for the recitation of the phrase "wherein the amount of the second component in the gel-phase lipid bilayer membrane is sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature, compared to a second percentage of active agent released in the absence of the second component," in claims 66 and 70 can be found for example at page 13, lines 17-21. Support for the recitation of the temperature range in claim 66 and 70 can be found, for example, at page 11, lines 14-16 and in Figures 4 and 8. Support for claim 71 can be found, for example, at page 14, lines 7-8. Support for claim 72 and 75 can be found, for example, in the paragraph bridging pages 13 and 14. Support for claim 73-74 can be found, for example, at page 14, lines 9-12. Support for claim 76 can be found, for example, at page 11, lines 3-5. Support for claims 76-77 can be found, for example, at page 13, lines 32-34. No new matter is added.

Claim Rejections - 35 U.S.C. §112, Second Paragraph

Claims 38-42 and 57-65 stood rejected under 35 U.S.C. §112, second paragraph, based on an assertion that certain terms in the claim rendered the claims insufficient to particularly point out and distinctly claim the subject matter that the applicant regards as the invention.

The Office Action alleged that the certain terms, "second," "third," and "material" in claims 38 and 39 rendered the claims confusing. Furthermore, the Office Action suggested that Applicants name the components referred to in the claim in a Markush format.

Without conceding the correctness of the rejection, Applicant has cancelled claims 38 and 39 and presented the subject matter in new claim 66. Applicant submits that the newly presented claim obviates the alleged basis for the objection.

The Office Action objected to the term "produced by another method in claim 57."

Without conceding the correctness of the rejection, Applicant has amended claim 57 to delete the objected language, thereby rendering the rejection moot.

The Office Action also suggested that claim 60 be revised to recite specific surface active agents to clarify the claim. In addition, the Office Action alleged that certain terms in claim 61 rendered the claims unclear.

Applicant has amended claim 60 to include a recitation of surface active agents in a Markush format. In addition, claim 61 has been amended to delete the objected terms.

The Office Action posited that the claim 57 was unclear.

Without conceding the correctness of the rejection, Applicant has cancelled claim 57.

In light of the above-described amendments to the claims, the asserted basis for the rejection is moot. Reconsideration is respectfully requested.

Claim Rejections - 35 U.S.C. §102

A. Claims 38-40, 42 and 65 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Uster et al (U.S. Patent No. 4,828,837). The Office Action notes compositions containing lysophosphatidic acid (second component) and phosphatidic acid (phospholipids) and the drug, minoxidil (third component) in Uster et al.

Without conceding the correctness of the rejection, Applicant has rewritten the above claims to more particularly and distinctly claim the subject matter of his invention. Applicant submits that the claims are allowable because Uster et al. lacks the composition as claimed in the new claims. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

B. Claims 38-40, 42 and 65 stood rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Radhakrishnan et al (U.S. Patent No. 4,906,476). The Office Action notes compositions containing a lysolipid (second component) and a phospholipids (third component) for the delivery of steroids such as prednisone in Radhakrishnan et al. In particular, the Office Action cites the Abstract and Example 1.

Reconsideration and withdrawal of the rejection is respectfully requested. Applicant notes that the liposomes prepared in Example 1 were rehydrated at 30 °C (col. 16, lines 6-10). As will be apparent to those of skill in the art (see Exhibit A, Mayer, Madden, Bally, Cullis. Mayer, L., et al., pH gradient-mediated drug entrapment in liposomes, in Liposome Technology, 2nd ed., G. Gregoriadis, Editor. 1993, CRC Press, Tokyo. p. 30, and Fettiplace, R.; Haydon, D.A. *Physiological Reviews*, 1980, 60, p. 528), lipid will not rehydrate substantially in its gel phase, indicating that the partially hydrogenated egg phosphatidyl choline in the example must be in its liquid phase at 30 °C (or above). Therefore, the liposomes prepared in Example 1 of the reference are in their liquid phase, and not in the gel-phase as required by Applicant's claimed liposome. Accordingly, the rejection over Radhakrishnan et al. cannot stand.

C. Claims 38-40 are rejected under 35 U.S.C. §102 for allegedly being anticipated by DAUC (abstract of Japanese disclosure). In particular the Office Action asserts that DAUC discloses liposomal preparations that contain phosphatidylcholine, ethanolamine, inositol, lysophosphatidylcholine, lecithin, sugar lipids, surfactants and mixtures thereof. Furthermore, the Office Action posits that a method is disclosed that is conducted by hydrating the lipid with an aqueous solution at temperatures higher than the phase transition temperature. The liposomes contain active agents such as anti-tumor agents, antibiotics, proteins, polysaccharides, vitamins and other medicinals.

Applicant respectfully disagrees. A claim is anticipated only if each and every element is found, either expressly or inherently described, in the reference (*see* MPEP 2131). Applicant's invention provides liposomes that are stable in the gel phase, and do not release their contents at normal body temperature. The inclusion of the second component in the liposome bilayer significantly increases the amount of the active agents released from the liposome at the gel-to liquid crystalline phase transition temperature, than the amount of the active agents that would be released in the absence of the second component.

DAUC fails to disclose the temperature at which the active agent is released from the liposome. Moreover the reference fails to disclose the desirability of liposome compositions that release the active agent at 39 to 45 °C. In fact, in the example described in the abstract, the phase transition temperature of the exemplified liposome preparation is 23 °C. Such a liposome would therefore not have a gel-phase bilayer membrane at normal body temperatures.

Accordingly, reconsideration of the rejection is respectfully requested.

D. Claims 38-40, 42 and 65 stand rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Ogawa (U.S. Patent No. 5,094,854). Specifically, the Office Action asserts that Office Action discloses liposome compositions containing drugs for hyperthermia therapy. The Office Action purports that the liposomes disclosed in the reference contain a mixture of lipids that includes the claimed combination and various drugs.

Applicant respectfully disagrees. Applicant's invention provides liposomes that are stable in the gel phase, and do not release their contents at normal body temperature. The inclusion of the second component in the liposome bilayer significantly increases the amount of the active agents released from the liposome at the gel-to liquid crystalline phase transition temperature, than the amount that would be released in the absence of the lysolipid. For instance, the amount of 6-carboxyfluorescein (CF) released from liposomes near the phase transition temperature in Example 2 and Figure 4 of the instant application illustrate this property. Liposomes that have a bilayer of pure DPPC become unstable near the phase transition temperature, causing release of some of the CF. However, only about 20% of the contents of the liposome are released at or slightly above the phase transition temperature. In contrast, liposomes that contain, for example, 10 mole % of MPPC (second component) and 90 mole % DPPC release significantly more active agent: about 80% of the CF is released at or slightly above the phase transition temperature. Thus, the amount of CF released from liposomes of the invention is increased by a factor of 4 over the amount released from liposomes having a bilayer of pure DPPC. This property is advantageous for preferential delivery of active agent to diseased sites, as opposed to slow release of active agents from liposomes.

The claims are allowable because Ogawa lacks the liposome composition of Applicant's amended claims. Specifically, the reference does not teach liposomal preparations that include the second components as recited in Applicant's amended claims. Moreover, there is no

teaching of the desirability of modifying the liposomal compositions of Ogawa by inclusion of the recited second components in the bilayer membrane to increase the percentage of active agent released from the liposome at the phase transition temperature as described in Applicant's claims.

Reconsideration and withdrawal of the rejection is respectfully requested.

E. Claims 38-40, 42 and 65 are rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Eibl (U.S. Patent No. 5,626,867). The Office Action alleges that Eibl discloses liposomal formulations that include DPPC and DSPA. The liposomes contain a variety of active agents including anti-tumor agents.

Applicant respectfully disagrees. Applicant submits that the instant claims are allowable because Eibl fails to disclose a second component. Although the Office Action alleges that DSPA is a second component, DSPA is distinguished from the second components specified in claim 66 (e.g., DSPA is not a lysolipid). Thus, the invention as particularly and distinctly defined in the claims is neither disclosed nor suggested by the prior art of record. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

F. Claims 38-42 and 65 are rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Alving (U.S. Patent No. 4,416,872). The Office Action alleges that Alving discloses liposomal formulations that include DPPC and ceramide.

Applicants respectfully disagree. Applicant submits that the new claims describe liposomes wherein the active agent is rapidly released from the liposome at 39 to 45 °C. It is noted that Alving neither teaches nor suggests a composition having this feature (i.e., or its utility in hyperthermic therapy). In facts, Alving teaches away from the advantages of claimed liposomal compositions. In contrast to the features of the claimed liposomes, the liposomes of Alving emphasize the slow effectiveness through slow biodegradation of the multilamellar membrane structure of the liposome (see, for example, col. 2, lines 47-50). Absent a teaching of this feature, the rejection cannot stand. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim Rejections - 35 U.S.C. §103

A. Claims 38-40, 42 and 65 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Hristova. The Office Action contends that Hristova discloses liposomal compositions containing dipalmitoylphosphatidylcholine and lysolipid in instant amounts, and PEG derivatized lipids. The Office Action notes that the references disclose the effect of lysolipids in general on gel phase bilayers and the use of monooleoylphosphatidylcholine in particular. The Office Action asserts that it would have been obvious to those of ordinary skill in the art to use any lysophosphatidylcholine with the expectation of obtaining similar effects on the gel phase bilayers.

Applicants respectfully disagree. Applicant submits that the new claims describe liposomes wherein the active agent is released from the liposome at 39 to 45 °C. It is noted that Hristova neither teaches nor suggests a composition having this feature (i.e., or its utility in hyperthermic therapy). Absent a teaching of this feature, the rejection cannot stand. Reconsideration and withdrawal of the rejection is respectfully requested.

B. Claims 57-64 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Uster, Radhakrishnan or DAUC or Ogawa or Eibl or Alving further in view of Mayer et al. or Boman et al. The Office Action submits that Uster, Radhakrishnan or DAUC or Ogawa or Eibl or Alving lack teachings of the loading of drugs by a pH gradient, but notes that the references all teach classical methods of preparation of liposomes. Mayer et al. discloses the loading of drugs into liposomes using pH gradients to achieve high trapping efficiencies. Boman, similarly discloses trapping and retention of drugs, e.g., vincristine using pH gradients. The Office Action asserts that loading drugs into the liposomes of Uster, Radhakrishnan or DAUC or Ogawa or Eibl or Alving using a pH gradient would have been obvious in view of Mayer et al. and Boman et al.

Applicants respectfully disagree. Applicant's claimed method is directed to a method of loading active agents into a liposome comprising a gel-phase lipid bilayer, with the lipid bilayer comprising phospholipid. The lipid bilayer is present at a temperature below its phase transition temperature. It is then exposed to an active agent such that the active agent passes into and through the lipid bilayer, entering the liposome interior. The method allows for an increase in the percentage of active agent released at the phase transition temperature of the liposome membrane.

Uster fails to disclose or suggest Applicant's claimed method because it fails to describe loading a liposome having a gel-phase lipid bilayer at a temperature below its phase transition temperature. Uster describes forming the liposomes by preparing a solution of lipid, amphipath and minoxidil; drying the solution to a thin film; and hydrating in a suitable buffer solution. Alternatively, a film of lipids can be hydrated with a solution containing a non-crystalline minoxidil composition (See col. 7, line 47-60).

Similarly, Radhakrishnan fails to teach or suggest the claimed method because it fails to describe loading a liposome having a gel-phase lipid bilayer at a temperature below its phase transition temperature. Here again, the liposomes are loaded with active agent by combining the lipid and active agent (BDP) in chloroform, drying the solution to a thin film; and hydrating in a buffer solution. See Example 1 on col. 15 and 16 of Radhakrishnan.

DAUC fails to suggest the claimed method, because the method described in the abstract is prepared at a temperature higher than its phase transition temperature. (See the first paragraph of the abstract).

Ogawa fails to disclose or suggest loading the liposomes at a temperature below the phase transition temperature of the liposome. Examples 1, 8 and 11 of Ogawa describe forming water/oil emulsion containing organic solvent, lipid, active agent (CDDP) and saline and evaporating off the organic solvent.

Eibl et al. fails to disclose or suggest a method of loading a gel-phase liposome at a temperature below the phase transition temperature of the liposome. Similarly, Alving et al. fails to disclose a temperature at which the liposomes are loaded with active agent.

Mayer et al. also fails to disclose or suggest loading below the phase transition temperature of gel phase bilayer. The Office Action asserts that the abstract suggests loading of liposomes at room temperature. Applicant respectfully notes that disclosure of the temperature at which loading is conducted is absent from the abstract.

Boman et al. fails to disclose or suggest liposomes having bilayer membranes that have a phase transition temperature. As noted in the Materials and Method section, the liposomes had a phosphatidylcholine/cholesterol molar ratio of 55:45. Incorporation of such high levels of cholesterol in the lipid bilayer results in the elimination of the phase transition from the gel to liquid crystalline phase. See, for example, p. 452 second column (first full paragraph) of Vist et al. (Exhibit B, Vist, MR; Davis, JH *Biochemistry* **1990**, *29*, 451-464). The Conclusions section

of Vist et al. notes that at concentrations >22 mol.% cholesterol, a β-phase is found in the membranes. The β-phase resembles the Lα phase (which is a fluid phase, and not a gel-phase) in lateral diffusion rate and rotational diffusion rate.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting

A. *Claims 1-12 of U.S. Patent No. 5,827,533*

Claims 38-42 and 65 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,827,533. The Office Action submits that the claims are not identical, but alleges that the claims are not patentably distinct from each other because the instant "comprising" does not exclude cholesterol recited in the patented claims.

Applicant respectfully disagrees. First, Applicant notes that claim 38 has been rewritten as new claim 66. Second, the claims of U.S. Patent No. 5,827,533 ("the '533 patent") fail to teach or suggest a liposome having a gel-phase lipid bilayer membrane containing a second component (e.g., surface active agent, active agent) in an amount sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature, compared to a second percentage of active agent released in the absence of the second component. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. *Claims 1-15 and 24 of U.S. Patent No. 6,200,598*

Claims 38-42 and 65 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38-42 and 65 of U.S. Patent No. 6,200,598. The Office Action submits that the claims are not identical, but alleges that the claims are not patentably distinct from each other because the instant generic claims include the specific components and the ratios recited in the claims of said patent.

Without conceding the correctness of the rejection, Applicant has submitted a terminal disclaimer. Reconsideration and withdrawal of the rejection are respectfully requested.

C. *Claims 1-31 of U.S. Patent No. 5,882,679*

Claims 38-42 and 65 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-31 of U.S. Patent No. 5,882,679. The Office Action submits that the claims are not identical, but alleges that the claims are not patentably distinct from each other because the instant generic claims include the specific percentages of the lipid-polymer recited in the claims of said patent.

Applicant respectfully disagrees. First, Applicant notes that claim 38 has been rewritten as new claim 66. Second, the claims of U.S. Patent No. 5,882,679 ("the '679 patent") fail to teach or suggest a liposome having a gel-phase lipid bilayer membrane containing a second component (e.g., surface active agent, active agent), where the second component is present in the gel-phase lipid bilayer membrane in an amount sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature, compared to a second percentage of active agent released in the absence of the second component. Furthermore, the claims of the '679 application fail to teach or suggest a gel-phase lipid bilayer having a phase transition temperature of 39 to 45 °C. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

D. *Claims 1-14 of U.S. Patent No. 6,143,321*

Claims 38-42 and 65 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,143,321. The Office Action submits that the claims are not identical, but alleges that the claims are not patentably distinct from each other because the instant generic claims include the specific amount of surface active agents in the patented claims.

Applicant respectfully disagrees. First, Applicant notes that claim 38 has been rewritten as new claim 66. Second, the claims of U.S. Patent No. 6,143,321 ("the '321 patent") fail to teach or suggest a liposome having a gel-phase lipid bilayer membrane containing a second component (e.g., surface active agent, active agent), where the second component is present in the gel-phase lipid bilayer membrane in an amount sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature, compared to a second percentage of active agent released in the absence of the second component. Furthermore, the claims of the '321 application fail to teach or suggest a gel-phase lipid bilayer

having a phase transition temperature of 39 to 45 °C. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Specification

The specification has been amended in the paragraph at page 9, lines 16-22 to correct an obvious error. No new matter is added. Entry of the amendment to the specification into the record is respectfully requested.

☒ If an extension of time is deemed required for consideration of this paper, please consider this paper to comprise a petition for such an extension of time; The Commissioner is hereby authorized to charge the fee for any such extension to Deposit Account No. 04-0480.

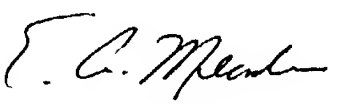
and/or

☒ If any additional fee is required for consideration of this paper, please charge Account No. 04-0480.

Closing Remarks

Applicant thanks the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration in view of this response and allowance of the pending claims are earnestly solicited.

Respectfully submitted,



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